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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/621,254 | 07/14/2003 | Steven W. Dow | 2880 | 9736 |

20350 7590 03/14/2008

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| EXAMINER | |
|---|---|
| HOLLERAN, ANNE L | |
| **ART UNIT** | **PAPER NUMBER** |
| 1643 | |

| MAIL DATE | DELIVERY MODE |
|---|---|
| 03/14/2008 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/621,254 | DOW ET AL. | |
| | Examiner | Art Unit | |
| | ANNE L. HOLLERAN | 1643 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *16 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *8,19 and 157* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,10,31-36,38-40,42-45,47,50-52,55-68,85-87,112-121 and 152-156* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/07, 3/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 1-8,10,19,31-36,38-40,42-45,47,50-52,55-68,85-87,112-121 and 152-157.

## DETAILED ACTION

1. The amendment filed November 16, 2007 and the supplemental response filed 12/19/2007 are acknowledged.

2. Claims 1-8, 10, 19, 31-36, 38-40, 42-45, 47, 50-52, 55-68, 85-87, 112-121, and 152-157 are pending.

Claims 8, 19, and 157 drawn to non-elected inventions, are withdrawn from consideration. Claim 8 is drawn to a method that includes "down regulating an immune response", which does not appear to be a step that is contemplated in the treatment of a subject with cancer.

Claims 1-7, 10, 31-36, 38-40, 42-45, 47, 50-52, 55-68, 85-87, 112-121, and 152-156 are examined on the merits.

***Claim Rejections Withdrawn:***

***Claim Rejections - 35 USC § 112***

3. The rejection of claims 6, 7, 9, 31-45, 47, 50-52, 55-68, 112-121, 151, 152 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of the amendments to the claims.

4. The rejection of claims 9, 10, 112-121 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of treating a subject having cancer, does not reasonably provide enablement for methods of preventing cancer in a subject is withdrawn in view of the amendment to the claims.

5. The rejection of claims 1-7, 31-45, 47, 50-52, 55-68, 85, 151-156 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in view of the amendments to the claims.

***Claim Rejections - 35 USC § 102***

6. The rejection of claims 1-7, 9, 10, 31-33, 41, 52, 61, 63, 64, 85-87, 112-117, 118, 119, 121, 151-155 under 35 U.S.C. 102(b) as being anticipated by Milas (Milas, L., Develop. biol. Standard., 38: 301-306, 1978) as evidenced by Hacker (Hacker, G. et al. Immunology, 105: 245-251, 2002, March) is withdrawn in view of the amendments to the claims limiting the delivery vehicle to that which comprises a liposome, wherein the liposome is positively charged, negatively charged or is neutral.

7. The rejection of claims 1-7, 9, 10, 31-34, 41-45, 52, 61, 64, 65, 85-87, 112, 113, 118, 119-121, 151, and 156 under 35 U.S.C. 102(e) as being anticipated by Raz (US 6,534,062; issued Mar. 18, 2003; effective filing date is July 5, 2000) is withdrawn in view of the amendment to the claims.

***Claim Rejections - 35 USC § 103***

8. The rejection of claims 1-7, 9, 10, 31-33, 41, 42, 52, 61, 64, 65, 85-87,112, 118, 119, 121, 151, and 156 under 35 U.S.C. 103(a) as being unpatentable over Davis (US 6,406,705; issued June 18, 2002; effective filing date June 3, 1999) is withdrawn.

9. The rejection of claims 1, 31, 60-62 under 35 U.S.C. 103(a) as being unpatentable over Raz (supra) in view of Maes (US 3,725,545; issued Apr. 3, 1973) is withdrawn in view of the amendments to the claims.

***Claim Rejections Maintained and New Grounds of Rejection:***

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1-7, 10, 31-36, 38-40, 42-45, 47, 50-52, 55-68, 85-87, 112-121, 152-156 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of treatment of a subject with cancer comprising administering a composition comprising a pattern recognition receptor ligand and a delivery vehicle comprising a liposome, where the liposome is a positively charged liposome, does not reasonably provide enablement for methods comprising the administration of a composition comprising a pattern recognition receptor ligand and a delivery vehicle comprising a liposome where the liposome is a neutral liposome or a negatively charged liposome. The specification does not enable any person skilled

in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation would be required to practice the full scope of the claimed inventions are: 1) quantity of experimentation necessary; 2) the amount of direction or guidance presented in the specification; 3) the presence or absence of working examples; 4) the nature of the invention; 5) the state of the prior art; 6) the relative skill of those in the art; 7) the predictability or unpredictability of the art; and 8) the breadth of the claims. See In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

The claims are drawn to in vivo methods of treatment comprising administering a ligand such as nucleic acid, where the ligand is a pattern recognition receptor ligand, and where the ligand is complexed with a delivery vehicle that is a cationic liposome, a neutral liposome or a negatively charged liposome.

The nature of the invention appears to be the activation of the innate immune system (that which recognizes pattern recognition receptor ligands) for the purpose of decreasing tumor volume in a subject with cancer. Thus, the administration of the ligand should be appropriate for the activation of the innate immune system, which according to the specification involves cells such as macrophages and natural killer (NK) cells.

The prior art recognizes that ligands such as nucleic acids are immunostimulatory and also immunostimulatory to macrophages (see prior art of record, such as Dow; US 6,693,086 to Dow; US 6,534,062 to Raz; Whitmore). Furthermore, the prior art teaches that cationic liposomes appear to increase the immune stimulatory action of nucleic acid ligands (see Dow or Whitmore). Additionally the prior art teaches that cationic liposomes are useful for increasing

the stability of nucleic acids, which are negatively charged and that cationic liposomes play a role in the uptake of the liposomal nucleic acids into macrophages (see Stuart, D.D., et al., Biochimical et Biohysica Acta, 1463: 219-229, 2000; page 219-220). Furthermore, it appears from the teachings of Stuart that the use of neutral liposomes or negatively charged liposomes will inhibit the immune stimulating activity of nucleic acids, either by decreasing stability of nucleic acids in serum or by inhibiting the uptake of the liposomes by the relevant cells.

The specification provides working examples limited to cationic liposomes (positively charged liposomes) and fails to provide a rationale for using other liposomes such as neutral or negatively charged liposomes.

In view of the teachings of the prior art which appear to show that cationic liposomes are useful for increasing the immunogenicity of nucleic acids and in view of the fact that neutral or negatively charged liposomes might decrease the immunogencity of nucleic acids, and further in view of the lack of specific teachings in the specification concerning the utility of neutral or negatively charged liposomes with respect to encapsulating nucleic acids for the purpose of increasing their immune stimulatory activity, the specification does not enable the use of neutral or negatively charged liposomes in methods for the treatment of cancer comprising the administration of a pattern recognition receptor ligand such as a nucleic acid. One of skill in the art would have to engage in undue experimentation to make and use the claimed methods with respect to the use of immunostimulatory nucleic acids for the treatment of cancer, because the purpose of administering the nucleic acid ligands is to activate the innate immune system and the use of neutral or negatively charge liposomes would interfere with this process.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 1-7, 10, 31-36, 39, 40, 42, 43-44, 61, 64, 65, 85-87, 112, 118, 120, 151, and 156 under 35 U.S.C. 103(a) remain/are rejected as being obvious over Dow (US 6,693,086; issued

Feb. 17, 2004; effective filing date, June 25, 1998) in view of Milas (supra). This rejection is newly applied to claims 6, 7, 10, 42, 86 and 87.

The declaration under 37 CFR 1.132 filed Nov. 16, 2007 is insufficient to overcome the rejection of claims 1-5, 31-37, 39, 40, 43-44, 61, 64, 65, 85, 112, 118, 120, 151, and 156 based upon the fact that Dow (US 6,693,086) is a reference available under 102(e) because it is a patent to another as set forth in the last Office action because: The statements provided in the declaration assert that Stephen Dow was the inventor of the invention which was disclosed but not claimed in US 6,693,086. However, these statements do not establish that the inventor disclosed but not claimed was derived by the inventor of this application, because the inventor of this application is the inventive entity of Stephen W. Dow and Jeffrey Fairman. Therefore, the invention disclosed but not claimed appears to be an invention "by another". Therefore, the rejection is maintained for the reasons of record, which are reitered below:

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in

accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

Dow teaches methods for treating cancer comprising the administration of immunostimulatory nucleic acids complexed with liposomes, such as the liposomes as recited in claims 34-37 (see column 6, lines 41-58). Dow teaches a method that can elicit a systemic, anti-tumor immune response in a mammal that results in an increase in effector cell activity and particularly natural killer cell activity and an increased production if interferon gamma (see column 3, lines 8-25). Dow teaches that the nucleic acid may be any nucleic acid, coding or non-coding, and not necessarily operatively linked to a transcription control sequence (see column 13, lines 14-29). Dow also teaches the use of a recombinant nucleic acid (reads on synthetic DNA) (see column 13, lines 34-35). Dow teaches administering the compositions comprising immunostimulatory nucleic acids complexed with liposomes to cancer patients, but fails to explicitly teach administering to cancer patients that are also receiving radiation therapy. Dow fails to teach methods comprising the further administration of radiation therapy.

However, the method of Dow is a method of treating cancer by stimulating the immune system of the subject to attack the subject's cancer, and Milas teaches that in cases where there is a large tumor burden, that immunotherapeutic methods may not be sufficient. Thus, Milas teaches combining an immunotherapeutic method with radiation therapy to increase the effectiveness of an immunotherapeutic method. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the

methods of Dow to stimulate the immune system of a cancer patient for the purpose of treating the cancer and to modify the method of Dow by combining Dow's method with radiation therapy as suggested by Milas. One would have been motivated by the teachings of Milas that methods of treating cancer by immunotherapy may be enhanced by combining with radiation therapy.

12. Claims 1-7, 10, 31-36, 39, 40, 42-45, 52, 61, 64, 65, 85-87, 112, 113, 118-120, 151, and 156 under 35 U.S.C. 103(a) as being unpatentable over Raz (US 6,534,062; issued Mar. 18, 2003; effective filing date is July 5, 2000) in view of Whitmore (Whitmore, M. et al. Gene Therapy, 6: 1867-1875, 1999) or Dow (Dow, S.W. , et al. The Journal of Immunology, 163: 1552-1561, 1999).

Raz teaches a method comprising the administration of an immunostimulatory nucleic acid and subjecting the subject to radiation, because Raz teaches that the composition comprising the immunostimulatory nucleic acid may be administered to a cancer patient that has undergone radiation therapy (see claim 8, column 46). Raz teaches delivery vehicles that are liposomal and non-liposomal (see column 24, line 61 – column 26, line 42). Raz teaches combination therapy, which includes various examples of chemotherapy (see column 26, line 60 to column 27, line 39).

Raz fails to explicitly describe the nature of the liposomes that are used as delivery vehicles.

However the use of cationic liposomes for the delivery of nucleic acids is known in the art as evidenced by the teachings of either Whitmore or Dow (see abstracts; and page 1873, 1st to 2nd column for Whitmore, and page 1553, 1st column for Dow).

Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have combined the teachings of Raz with that of either Whitmore or Dow to make the claimed methods because Raz teaches the method of treating cancer by administering a combination of radiation and immunostimulatory nucleic acids in liposomes and because either Whitmore or Dow teaches that cationic liposomes increase the immune stimulatory effect of nucleic acids.

13. Claims 1, 31, 61 and 62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Raz (supra)in view of either Whitmore (supra) or Dow (supra) in view of Maes (US 3,725,545; issued Apr. 3, 1973).

Within the scope of claims 1, 31 and 60-62 are methods where the ligand is an oligonucleotide that comprises at least one of poly I:C or related poly I:C oligonucleotides.

Raz fails to explicitly teach immunostimulatory nucleic acids that are poly I:C oligonucleotides or related poly I:C oligonucleotides. However, Maes teaches methods for potentiating antibody producing ability of nucleic acid containing preparations where the nucleic acid is polyinosinic acid, or poly I:C (see column 6, lines 26-62). Also, it is noted that Dow employs poly(I:C) nucleic acids (see Figure 5, for example). Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the nucleic acids of Maes in the method of Raz, because Maes teaches polyinosinic acid are immunostimulatory oligonuceotides (have antibody producing ability). One would have been motivated to use the method of Raz in combination with either Dow or Whitmore together with

the method of Maes because both are methods directed to increasing the functionality of the immune system with respect to polynucleotides.

***Conclusion***

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne Holleran, whose telephone number is (571) 272-0833. The examiner can normally be reached on Monday through Friday from 9:30 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached on (571) 272-0832. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Official Fax number for Group 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Anne L. Holleran
Patent Examiner
March 3, 2008

/Alana M. Harris, Ph.D./
Primary Examiner, Art Unit 1643